64. (Previously presented): The bioreactor of claim 45, wherein the stream of substance comprises a substance affecting the growth of biological cells.

65. (Previously presented): The bioreactor of claim 45, wherein sidewalls at the intersections of the first connection channel with the chamber and the second connection channel with the chamber are tapered to form an angle of inclination between about 10 and 45 degrees from vertical and an enclosed angle between about 30 and 80 degrees.

Main Points for Discussion:

1. **In the June 23, 2008 Office Action, claim 45 was rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.**

   In response, claim 45 has been amended to read, in part, "in a direction that is substantially parallel to the plane of *the first surface of* the first substrate." It is now believed that this rejection has been overcome.

2. **Claims 44-49 and 58-65 were rejected in the June 23, 2008 Office Action as being rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent no. 4,201,845 to Feder et al. (hereinafter "Feder"). Applicants respectfully traverse these rejections for at least the following reasons:**

   ***Claim 44*:**

   Among other unique limitations, independent claim 44 as previously presented recites a bioreactor having "...confining means positioned in the chamber to form a confinement region to confine the biological cells therein with the liquid medium, ***wherein the chamber, the inlet portion, the first connection channel, the outlet port, and the second connection channel are all formed in the first substrate***." As shown in **Fig. 2A1** as originally filed (attached to this communication), the bioreactor 1000 has chamber 1006, first connection channel 1021, second connection channel 1005, inlet port 1021, and outlet port 1005, which are ***all formed in the first substrate 1001***.

   In contrast, as specifically shown in **Figs. 2 and 3**, Feder discloses a ***macroscopic*** device that is assembled in multiple layers requiring fastening together with bolts and nuts and pipe. **Fig. 2** shows nuts 22 and bolts 37 which are used for connecting the ***separate, detachably joined parts*** upper part of the housing 13 with the lower part of the housing 12.

   With specific regard to the Primary Examiner's statement that "Part (12) is equivalent to applicant's claimed first substrate," applicant respectfully submits that in Feder, the ***cells***

grow on the hollow fibers that are contained within the chamber, and hence, Feder's part 12 is clearly not equivalent to the first substrate of the present invention.

Therefore, applicant respectfully submits that Feder does not disclose, teach, or suggest a bioreactor having "...confining means positioned in the chamber to form a confinement region to confine the biological cells therein with the liquid medium, ***wherein the chamber, the inlet portion, the first connection channel, the outlet port, and the second connection channel are all formed in the first substrate***" as recited in amended claim 45 of the present invention. (Emphasis added.)

With regard to integration of parts, see MPEP 2144.04, citing *Schenck v. Nortron Corp.*, 713 F.2d 782, 218 USPQ 698 (Fed. Cir. 1983) (Claims were directed to a vibratory testing machine (a hard-bearing wheel balancer) comprising a holding structure, a base structure, and a supporting means which form "a single integral and gaplessly continuous piece." Nortron argued that the invention is just making integral what had been made in four bolted pieces. The court found this argument unpersuasive and held that the claims were patentable because the prior art perceived a need for mechanisms to dampen resonance, whereas the inventor eliminated the need for dampening via the one-piece gapless support structure, showing insight that was contrary to the understandings and expectations of the art.).

In addition to the limitations discussed above, claim 44 also recites a bioreactor "...wherein the confining means comprises a ***first filter and a second filter***, wherein the first filter is positioned proximate to the first connection channel and the second filter is positioned proximate to the second connection channel, and the first filter and the second filter are substantially parallel to each other; and wherein ***each of the first filter and the second filter comprises a plurality of posts spaced apart from each other not to allow biological cells to pass through it***." (Emphasis added.)

As described in the specification as originally filed, for example, in paragraphs on page 25, lines 23-33 and shown in **Fig. 2C** (attached to this communication), the confining means "includes a ***first filter 1085a*** and a ***second filter 1085b***, where the first filter 1085a is positioned proximate to the first connection channel 1021 and the second filter 1085b is positioined proximate to the second connection channel 1005, and the first filter 1085a and the second filter 1085b are substatially parallel to each other. ***Each of the first filter 1085a and the second filter 1085b includes a plurality of posts 1086 spaced apart from each other not to allow cells to pass through it.***"

Applicant respectfully submits that Feder simply does not disclose, teach, or suggest a bioreactor having these limitations, and having all the other limitations as recited in amended independent claim 44.

For at least these reasons, previously presented independent claim 44 is patentable under 35 U.S.C. §103(a) over Feder.

Accordingly, claims 46-49, which depend from allowable previously prented claim 44, are also allowable for at least this reason.

Claim 45:

Among other unique limitations, claim 45, as amended, recites in part a bioreactor comprising "a first substrate,...an inlet port,...a first connection channel..., an outlet port, ...a second connection channel,... [and] a confining means ... wherein the chamber, the inlet portion, the first connection channel, the outlet port, and the second connection channel are all formed in the first substrate ***such that, in operation, the stream of substance flows from the inlet port through the first connection channel, the chamber, and the second connection channel to the outlet port in a direction that is substantially parallel to the first surface of the first substrate.***

As shown in **Figs. 2A1-2I** of the drawings as originally filed and described in the specification as originally filed, for example, in paragraphs on line 28-38 of page 18 and lines 7-18 of page 19, the bioreactor according to one embodiment of the present invention is a ***microfluidic*** device which integrates "suitable cell culture and microfabrication techniques to permit cell growth in ***small, confined, well perfused volumes*** at tissue densities, ***provide independent control of*** multiple chemokines and growth factor gradients, ***shear forces, tissue perfusion,*** and permeability of physical barriers to cellular migration, and allow detailed optical and electrochemical observation of normal and cancerous cells during cell migration, intravasation, extravasation , angiogenesis, and other cellular processes." (Emphasis added.)

In contrast, as discussed above, the disclosure of Feder is directed specifically at a class of bioreactor that is radically different from the present invention as claimed in amended claim 45. For instance, Feder states that "[i]n accordance with the present invention, cell culture apparatus for the growth of cells in vitro is provided ***which employs elongate, selectively permeable hollow fibers*** in a shallow layer configuration as a matrix for cell attachment on the outer surface of the fibers, and aeration of the cells by passage through the interior of said fibers and permeation of the membrane wall." Feder, Col. 2, lines 22-28. Specifically, as shown in **Figs. 2-4**, Feder discloses a ***macroscopic*** device that is assembles in multiple layers requiring fastening together with bolts and nuts and pipe.

In operation of Feder's device, "cell culture medium is ***fed into chamber 23 through inlet ports 26 and 27.*** The medium is inoculated through port 29 with a seed culture .... During the incubation, periodic changes of media can be made, with the spent medium ***being expelled through outlet port 28*** and fresh medium again being supplied through inlet ports 26 and 27. Samples of macromolecular materials can be ***withdrawn through access port 29*** at any desired time during the incubation. ***The culture medium flows into the lower part of chamber 23 beneath perforated plate 35 which thereby serves as manifold or distributor means*** to provide uniform distribution of the medium and ***a flow path which is upward and transverse to the plane of the elongate axes of the fibers.***" (Feder, col. 4, lines 56-68 through col. 5, lines 1-29, and Figs. 2 and 3) (Emphasis added.)

In other words, in Feder's device, the culture medium flows ***from the inlet ports 26 and 27, through the perforated plate 35 (or filter plate 40, Fig. 4) into the fiber layer 34, and then is expelled through outlet port 28, i.e., the flow of the culture medium is transverse to the planar region containing the cells,*** i.e. the bed of parallel hollow fibers.

Therefore, applicant respectfully submits that Feder does not teach, disclose, or suggest a microfabricated bioreactor having these limitations, and having all the other limitations recited in amended claim 45 of the present invention.

For at least these reasons, amended claim 45 is patentable under 35 U.S.C. §103(a) over Feder.

Accordingly, previously presented claims 58-65, which depend from now allowable amended claim 45, are also allowable for at least this reason.

3. **It is now believed that the application is in condition for allowance and such allowance is respectfully requested.**